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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Roy A. Gravel et al.

Art Unit: 1623

Serial No.: 10/607,712

Examiner: Not yet assigned

Filed: June 27, 2003

Customer No.: 21559

Title: HUMAN METHIONINE SYNTHASE: CLONING, AND METHODS  
FOR EVALUATING RISK OF NEURAL TUBE DEFECTS,  
CARDIOVASCULAR DISEASE, AND CANCER

Mail Stop Amendment  
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Applicants submit the references listed on the attached form PTO 1449, copies of which are enclosed.

Under 35 U.S.C. § 120, this application relies on the earlier filing date of application serial number 08/980,326, which was filed on November 26, 1997. The following references were submitted to and/or cited by the Office in the prior application and, therefore, copies of these references are not provided for this application:

Bannerjee et al., GenBank Accession No. J04975, 1993.

Boushey et al., "A Quantitative Assessment of Plasma Homocysteine as a Risk Factor for Vascular Disease. Probable Benefits of Increasing Folic Acid Intakes," *JAMA* 274:1049-1057, 1995.

Chen et al., "Purification and Kinetic Mechanism of a Mammalian Methionine Synthase from Pig Liver," *J. Biol. Chem.* 269:27193-27197, 1994.

Chen, L.H. et al., "Human Methionine Synthase: Cdna Cloning, Gene Localization and Expression," *J. Biol. Chem.*, 272:3628-3634, 1997.

Drennan et al., "How a Protein Binds B12: A 3.0 Å X-ray Structure of B12-binding Domains of Methionine Synthase," *Science* 266:1669-1674, 1994.

Fenton and Rosenberg, *The Metabolic and Molecular Bases of Inherited Disease*, McGraw-Hill, New York, pp. 3129-3149, 1995.

Fujii and Huennekens, "Activation of Methionine Synthetase by a Reduced Triphosphopyridine Nucleotide-dependent Flavoprotein System," *J. Biol. Chem.* 249:6745-6753, 1974.

Gulati et al., "Defects in Human Methionine Synthase in cblG Patients," *Hum. Molec. Genet.* 5:1859-1865, 1996.

LeClerc et al., GenBank Accession No. U71285, 1997.

Li et al., GenBank Accession No. U75743, 1997.

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Luschinsky et al., "Crystallization and Preliminary X-ray Diffraction Studies of the Cobalamin-binding Domain of Methionine Synthase from *Escherichia coli*," *J. Molec. Biol.* 225:557-560, 1992.

Marra et al., GenBank Accession No. W33307, 1996.

Mellman et al., "Genetic Control of Cobalamin Binding in Normal and Mutant Cells: Assignment of the Gene for 5-methyltetrahydrofolate: L-homocysteine S-methyltransferase to Human Chromosome 1," *Proc. Natl. Acad. Sci. USA* 76:405-409, 1979.

Mills et al., "Homocysteine Metabolism in Pregnancies Complicated by Neural-Tube Defects," *Lancet* 345:149-151, 1995.

Rosenblatt et al., *The Metabolic and Molecular Basis of Inherited Disease*, McGraw-Hill, New York, pp. 3111-3128, 1995.

Rosenblatt et al., "Altered Vitamin B<sub>12</sub> Metabolism in Fibroblasts from a Patient with Megaloblastic Anemia and Homocystinuria Due to a New Defect in Methionine Biosynthesis," *J. Clin. Invest.* 74:2149-2156, 1984.

Rozen et al., "Molecular Genetic Aspects of Hyperhomocysteinemia and its Relation to Folic Acid," *Clin. Invest. Med.* 19:171-178, 1996.

Schuh et al., "Homocystinuria and Megaloblastic Anemia Responsive to Vitamin B12 Therapy. An Inborn Error of Metabolism due to a Defect in Cobalamin Metabolism," *N. Engl. J. Med.* 310:686-690, 1984.

Sillaots et al. "Heterogeneity in cblG: Differential Retention of Cobalamin on Methionine Synthase," *Biochem. Med. Metab. Biol.* 47:242-249, 1992.

Stegers-Theunissen et al., "Maternal Hyperhomocysteinemia: A Risk Factor for Neural-tube Defects?" *Metab. Clin. Exp.* 43:1475-1480, 1994.

Watkins et al., "Genetic Heterogeneity Among Patients with Methylcobalamin Deficiency. Definition of Two Complementation Groups, cblE and cblG," *J. Clin. Invest.* 81:1690-1694, 1988.

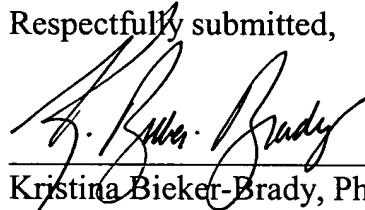
Watkins et al., "Functional Methionine Synthase Deficiency (cblE and cblG): Clinical and Biochemical Heterogeneity," *Am. J. Med. Genet.* 34:427-434, 1989.

Submission of this statement is not a representation that a search has been made nor is information included in this statement an admission that the information is material to patentability.

This statement is being filed before the receipt of a first Office action on the merits. Please apply any charges or credits to Deposit Account 03-2095.

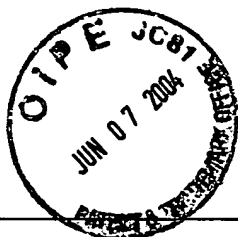
Date: June 3, 2004

Respectfully submitted,



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SUBSTITUTE FORM PTO-1449 (MODIFIED)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		Attorney Docket No. 50004/002005		
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use several sheets if necessary)		(37 C.F.R. § 1.98(b))		Serial No. 10/607,712		
				Applicants Roy A. Gravel et al.		
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				Group 1623		
				IDS Filed June 3, 2004		
				Customer No. 21559		
U.S. PATENTS						
Examiner's Initials	Patent Number	Issue Date	Patentee	Class	Subclass	Filing Date (If Appropriate)
	6,677,436	01/13/04	Sato et al.			
FOREIGN PATENT OR PUBLISHED FOREIGN PATENT APPLICATION						
Examiner's Initials	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation (Yes/No)
OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PLACE OF PUBLICATION)						
	Bannerjee et al., GenBank Accession No. J04975, 1993.					
	Boushey et al., "A Quantitative Assessment of Plasma Homocysteine as a Risk Factor for Vascular Disease. Probable Benefits of Increasing Folic Acid Intakes," <i>JAMA</i> 274:1049-1057, 1995.					
	Brasch et al., "Neonatal Megaloblastic Anemia Associated with Reduced Cellular Uptake of Folate and Low Methyl-B12 Levels: A New Mutation," <i>Aust. N. Z. J. Med.</i> 18 Supp. 434, 1988.					
	Chen et al., "Purification and Kinetic Mechanism of a Mammalian Methionine Synthase from Pig Liver," <i>J. Biol. Chem.</i> 269:27193-27197, 1994.					
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	Drennan et al., "How a Protein Binds B12: A 3.0 Å X-ray Structure of B12-binding Domains of Methionine Synthase," <i>Science</i> 266:1669-1674, 1994.					
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	Frosst et al., "A Candidate Genetic Risk Factor for Vascular Disease: A Common Mutation in Methylenetetrahydrofolate Reductase," <i>Nat. Genet.</i> 10:111-113, 1995.					
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	Goyette et al., "Human Methylenetetrahydrofolate Reductase: Isolation of cDNA, Mapping and Mutation Identification," <i>Nat. Genetics</i> 7:195-200, 1994.					
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	Leclerc et al., "Molecular Cloning, Expression and Physical Mapping of the Human Methionine Synthase Reductase Gene," <i>Gene</i> 240:75-88, 1999.					
EXAMINER			DATE CONSIDERED			
EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with the next communication to applicant.						

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	LeClerc et al., GenBank Accession No. U71285, 1997.					
	Leclerc et al., "Cloning and Mapping of a cDNA for Methionine Synthase Reductase, A Flavoprotein Defective in Patients with Homocystinuria," <i>Proc. Natl. Acad. Sci. USA</i> 95:3059-3064, 1998.					
	Li et al., GenBank Accession No. U75743, 1997.					
	Li et al., "Cloning, Mapping and RNA Analysis of the Human Methionine Synthase Gene," <i>Hum. Molec. Genet.</i> 5:1851-1858, 1996.					
	Luschinsky et al., "Crystallization and Preliminary X-ray Diffraction Studies of the Cobalamin-binding Domain of Methionine Synthase from <i>Escherichia coli</i> ," <i>J. Molec. Biol.</i> 225:557-560, 1992.					
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	Mills et al., "Homocysteine Metabolism in Pregnancies Complicated by Neural-Tube Defects," <i>Lancet</i> 345:149-151, 1995.					
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	Rosenblatt et al., "Prenatal Vitamin B <sub>12</sub> Therapy of a Fetus with Methylcobalamin Deficiency (Cobalamin E Disease)," <i>Lancet</i> 1:1127-1129, 1985.					
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	Sillaots et al. "Heterogeneity in cblG: Differential Retention of Cobalamin on Methionine Synthase," <i>Biochem. Med. Metab. Biol.</i> 47:242-249, 1992.					
	Steegers-Theunissen et al., "Maternal Hyperhomocysteinemia: A Risk Factor for Neural-tube Defects?" <i>Metab. Clin. Exp.</i> 43:1475-1480, 1994.					
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	Wilson et al., "Molecular Basis for Methionine Synthase Reductase Deficiency in Patients Belonging to the cblE Complementation Group of Disorders in Folate/Cobalamin Metabolism," <i>Hum. Molec. Genet.</i> 8:2009-2016, 1999.					
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